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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,033	08/01/2001	Rosanne M. Crooke	ISPH-0592	5785

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 10/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,033	CROOKE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-20 and 28* is/are pending in the application.

4a) Of the above claim(s) *15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14,20 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-13-2005, 9-12-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. The request for continued examination (RCE) filed 6-15-2005 was considered improper since prosecution was not closed in this application. As per MPEP section 706.07(h) [R-2], "If prosecution in the application is not closed, applicant will be notified of the improper RCE and any amendment/reply will be entered. Thereafter, the application will be forwarded to the examiner for consideration of the amendment/reply under 37 CFR 1.111."

2. Applicant's reply of 6-15-2005 is therefore considered a response to a Non-Final Office Action. Therefore, any new grounds of rejection applied in response to Applicant's amendment will be made final as necessitated by Applicant's amendment to the claims.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

4. The information disclosure statement of 9-12-05 is a duplicate of the IDS filed 6-13-2005.

Interview Summary

5. In the response filed 6-15-2005, Applicants stated on page 5, 1st paragraph, that it was determined during the interview of 5-18-2005 that amending the claims to recite "non-cleaving" in place of "non-catalytic" would be looked at favorably. However, it is noted that during this interview the examiner stated that particular amendments to the method claims shared with application 10/147,196 would be looked at favorably. Moreover, the Interview Summary of

5-18-2005 does not state that an amendment to the claims to recite "non-cleaving" would be looked at favorably.

Response to Amendment

6. The rejection of claims 1-2, 4-14 and 20-23 under 35 USC 103(a) as being unpatentable over Chan et al. (WO 01/12789 A2) is withdrawn in response to Applicant's amendment and arguments.

Claim Rejections - 35 USC § 112

7. The rejection of claims 1-2, 4-14, and 20-26 under 35 U.S.C. § 112 1st paragraph, lack of written description set forth in the Office Action of 1/19/2005, is withdrawn in response to Applicant's amendment.

8. Claims 1, 11, 20 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description/New Matter).

The instant claims recite "a *non-cleaving* compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein B, wherein said compound (1) specifically hybridizes to the nucleotide sequence set forth in SEQ ID NO: 3, and (2) demonstrates at least 30% inhibition of apoB expression when applied *in vitro* at a concentration of 150nM to HepG2 cells." In the response filed 6/15/2005, Applicants stated that the amendments to claims 1, 11, and 20 to recite, "non-cleaving" is supported by the disclosure of the specification

as filed (pg. 5). Applicants pointed to pg. 23, lines 34, to page 24, line 4. This portion of the specification describes how a region of an antisense oligonucleotide may serve as a substrate for RNase H, thereby providing support for a species of non-cleaving compounds that are antisense oligonucleotides that do not cleave. The claims, however, are drawn to a genus of non-cleaving *compounds* that is not limited to antisense oligonucleotides. Applicant has not pointed to a disclosure that is sufficient to provide support for the entire genus of non-cleaving compounds as now claimed.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-2, 4-5, 11-12, 14 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al.

The instant prior art is applied based upon the interpretation of "a non-cleaving compound 8 to 50 nucleobases in length" to read on an antisense oligonucleotide of 8 to 50 nucleobases in length, and not to a complex of antisense oligonucleotide and RNAse H, wherein RNAse H in this complex functions to cleave the target nucleic acid.

Tang et al. discloses an antisense compound that is 20 nucleotides in length targeting nucleotides 129 through 148 of SEQ ID NO: 3. This antisense

compound comprises a thiophosphorylation modification, see section 1.1. The antisense compound in a 0.9% salt solution was delivered to the culture medium of a culture of liver cells, wherein the culture comprises 10% fetal bovine serum and the microcarrier Cytodex-3.

Since the prior art structure of the antisense compound of Tang et al. meets all the structural limitations recite in the instant claims, absent evidence to the contrary, the prior art antisense compounds would also be expected to meet all the functional limitations recited in the instant claims, namely wherein said compound demonstrates at least 30% inhibition of apoB expression when applied *in vitro* at a concentration of 150nM to HepG2 cells. See for example, MPEP § 2112.01[R-2]II, wherein it states: "[P]roducts of identical composition can not have mutually exclusive properties."

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-2, 4-14, 20 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. in view of Cowsert (US Patent No. 5945290).

The discussion of Tang et al. as set forth above is incorporated here. However, Tang et al. does not teach wherein the antisense compound comprises at least one sugar or nucleobase modification, wherein the antisense compound

is a chimeric oligonucleotide, or wherein the antisense compound is in a colloidal dispersion system. Moreover, although Tang et al. teach that the antisense compounds are delivered in a saline solution it is unclear if the antisense compound in itself is a sodium salt, or pharmaceutically acceptable salt.

The prior art (Cowsert) teaches that antisense compounds may encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Preferred examples of pharmaceutically acceptable salts include salts formed with cations such as sodium, potassium, ammonium, magnesium, etc. (col. 10, lines 35-62).

Moreover, the Cowsert teaches that antisense compounds comprising 2'-O-methoxyethyl, 5-methylcytosine modifications, internucleoside linkage modifications, or wherein the antisense compound is a chimeric oligonucleotide, are preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid and increased nucleic acid stability in the presence of nucleases (see col. 5, lines 10-30, and col. 7-8, in particular, col. 8, lines 35-40; and col. 9, lines 34-44).

Additionally, Cowsert teaches the delivery of antisense compounds into cells comprising the use of a colloidal dispersion system. According to this reference colloidal dispersion systems may be used as delivery vehicles to enhance the in vivo stability of the compounds and/or to target the compounds to a particular organ, tissue or cell type (see bridging paragraph of col. 14-15).

It would have been obvious to the ordinary skilled artisan at the time of the instant invention to modify the teachings of Tang et al. with the teachings of Cowsert in the design of the instant invention. One of ordinary skill in the art would have been motivated to modify the antisense compound and compositions of Tang et al. to comprise, 5-methylcytosine, 2'-O-methoxyethyl modifications, a chimeric oligonucleotide, a colloidal dispersion, or pharmaceutically acceptable salts of the antisense compound, because Cowsert clearly teaches that antisense compounds and compositions comprising these modifications are preferred over native forms, since these modified antisense compounds have desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid and increased nucleic acid stability in the presence of nucleases (see col. 5, lines 10-30, and col. 7-8, in particular, col. 8, lines 35-40).

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the pro blem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Janet L. Epps-Ford
Examiner
Art Unit 1633

JLE